524,486

PCT/EP2003/009219

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M/43166-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/009219	International filing date (*day/month/year*) 20 August 2003 (20.08.2003)	Priority date (*day/month/year*) 20 August 2002 (20.08.2002)
International Patent Classification (IPC) or national classification and IPC C07D 401/14		
Applicant MERCKLE-GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 16 March 2004 (16.03.2004)	Date of completion of this report 10 September 2004 (10.09.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/009219

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-97, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-15, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of claim 15 in its present form. Patentability may also depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the medical use of a compound; it may, however, allow claims to the first medical application of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP 03/09219

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-15	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-15	NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims		NO

2. Citations and explanations

In this report, reference is made to the following documents, cited in the search report; the same numbering will be used throughout the procedure:

D1: US-A-6040320

D2: WO-A-2000017192

D3: EP-A-0004648

D4 Angewandte Chemie, International Edition (2002), 41(13), 2290-2293

D5: J. Med. Chem. (1999), 42, 2180-2190

D6: J. Med. Chem. (1996), 39, 3929-3937

D7: WO-A-9314081

D8: WO-A-2002066458

D9: DE-A-10114775.

The present application relates to 2-thio-substituted imidazole derivatives that bear a substituted 4-pyridyl ring as a substituent in position 4 of the imidazole ring and are unsubstituted at the N atom (NH). The application further relates to the use of said compounds to treat disorders of the immune system.

/...

1. Novelty (PCT Article 33(3))

None of the cited documents discloses compounds comprising the features "substituted 4-pyridyl ring", 2-thiomidazole" and "unsubstituted N atom". The requirement for novelty is therefore satisfied.

2. Inventive step (PCT Article 33(3))

2.1 Documents D1 to D3 disclose imidazole derivatives with anti-inflammatory activity. Compounds of the general formula I according to claim 1 of the present application are encompassed by the definitions of the general formulae disclosed in said documents (D1, formula I: R_1 = substituted phenyl, R_2 = substituted heteroaryl (e.g. halogen), R_3 = hydrogen, R_4 = $(A)_n-(CH_2)_q-X$ (A = sulphur) (columns 2-3); D2, formula (I): Het = optionally substituted pyridyl (3-amino-) (page 5, paragraph 2); Ar = 4-fluorophenyl (page 5, paragraph 4); D3, formula (I): R_1 and R_2 = an optionally substituted heteroaryl group and an optionally substituted aryl group, and R_3 = hydrogen (see abstract)).

Thus, from said documents, a person skilled in the art can immediately derive the technical teaching that compounds encompassed by the given formulae are suitable for solving the technical problem, namely that of providing imidazole derivatives with anti-inflammatory activity. Consequently, the provision of compounds according to the present claim 1 cannot at present be

/...

considered to involve an inventive step relative to documents D1 to D3.

In the event that a particular technical problem could be solved by the specific choice of substituents or substituent position, this must be demonstrated in an appropriate manner. In this respect, it should further be noted that the present application appears to provide a basis only for those compounds in which the pyridyl ring is substituted in position 2, and which have a substituted phenyl group in position 5 of the imidazole ring.

2.2 A person skilled in the art is aware from document D4 of compounds, from which the claimed compounds differ in that the pyridyl ring is substituted (page 2291, compounds 4 and 5). In addition, a person skilled in the art will learn from D4 that substituents in the place of the H atom of the imidazole ring can be tolerated (scheme 1). The relevant distinguishing feature therefore appears to have no influence on the presence of an inventive step.

The effect produced by the distinguishing feature "substituent on the pyridyl ring" does not appear to be clearly indicated in the present application. The technical problem addressed by the provision of compounds according to claim 1 can thus be regarded as no more than the provision of alternative compounds. However, for a person skilled in the art, compounds bearing the substituted pyridyl

/...

ring on the imidazole structure are known from D1 (table A, compound 78), D2 (page 5, last line of paragraph 2); D3 (page 2, lines 13-19), D5 (page 2181, table 1, compound 48; page 2183, diagram 6, compounds 45 and 46), D6 (page 3932, table 2, compounds 44 and 45) and D7 (page 9, lines 32-34). The use of these groups in compounds according to D4 (see above) therefore appears to be obvious in so far as no surprising effect resulting from this difference can be demonstrated.

2.3 Document D5 discloses compounds that differ from the claimed compounds by the nature of the substituent at position 2 of the imidazole ring (page 1283, compounds 45 and 46). The technical effect of this difference does not appear to be clearly indicated in the present application. Moreover, a person skilled in the art is aware of compounds comprising a substituent as per the present claim 1 (D1, D2, D3 and D4). Therefore, the provision of compounds which differ in this way from D5 cannot at present be considered inventive.

2.4 Document D6 discloses compounds from which the claimed compounds differ in that a thio substituent is present on the imidazole ring (D6, page 3932, table 2: compounds 44 and 45). (In the light of the disclosure of D4 (diagram 1), the substituent on the N atom appears to be of no significance.) However, 2-thio substituted compounds are known to a person skilled in the art (see above). No inventive step appears to be involved and, therefore, the variation of the disclosure of D6, as proposed in the present application, cannot be considered inventive either.

2.5 The dependent claims appear to contain no additional features that might form the basis for an inventive step. Independent claims 13 and 14 refer back to claim 1 and, therefore, no inventive step can be acknowledged in respect of the compounds therein defined either. In consequence, the application (claims 1-14) fails to meet the requirements of PCT Article 33(3).

2.7 Both the position of the substituents on the pyridine ring and also the nature of the substituents at position 5 of the imidazole ring appear to be significant in respect of the claimed subject matter. It would therefore appear appropriate to incorporate the corresponding features into an amended claim 1 (see examples in the application). Moreover, it should be made clear to what extent the respective distinguishing features, relative to the compounds disclosed in the prior art, can be used as the basis for an inventive step. In particular, any surprising effects resulting from these distinguishing features should be demonstrated."

3. Industrial applicability (PCT Article 33(4))

Acknowledged in respect of claims 1-14.

4. The exclusion of certain combinations of substituents (claim 1, page 99, line 25 ff.) is unclear (PCT Article 6).

/...

5. Documents D8 and D9 were published after the priority date of the present application but before the international filing date thereof. Should the priority of the present invention be invalid, the disclosure of said documents would, in consequence, be considered to belong to the prior art. Moreover, in the event of a European examination procedure, reference would be made to D8 for the purpose of assessing novelty.

6. Contrary to PCT Rule 5.1(a)(ii), the description does not cite documents D1 and D4 or indicate the relevant prior art disclosed therein.